

## Editorials

# Biopsy diagnosis of prostatic cancer—current areas of concern

Prostate specific antigen (PSA) has been recognised as a serum marker with the potential for early detection of prostate cancer—the second most frequent cause of tumour death in men. Transrectal ultrasound (TRUS) allows sampling of specific sites within the prostate gland, and surgical innovation has made radical prostatectomy more acceptable to patients. These events have produced a major increase in prostatic needle biopsies taken with the aim of diagnosing cancer at a stage when radical treatment may be curative.

Pilot schemes for prostatic carcinoma screening,<sup>1</sup> include studies completed in England,<sup>2</sup> but there is no nationally funded project. Arguments against screening include: limited knowledge on the sensitivity and specificity of detection techniques (biopsy cannot be justified in asymptomatic patients with a normal serum PSA and digital rectal examination); limited reliability of prognostic factors for disease at diagnosis; and disagreement on the best treatment, indeed whether any form of therapy for screen detected cancer saves lives. The PIVOT (Prostate Cancer Intervention Versus Observation Trial) and PLCO (Prostate, Lung, Colo-rectal and Ovarian Trial) underway in United States and a similar European study may answer these questions in 10–12 years.<sup>3</sup>

In support of PSA based screening are series showing an increase in the proportion of organ confined cancers compared with the unscreened population.<sup>1</sup> Moreover, diagnosis at this stage may allow the question of curative treatment to be answered. If screening is to be evaluated this will have to be organised before the control population disappears in the enthusiasm for case finding. The existence of known high risk groups (those with a family history of prostate cancer, especially when younger than 55 years old, and people of West African and Caribbean origin) prompts consideration of selective screening. Meanwhile, in Britain we have case finding of variable intensity which is largely unmonitored.

The optimum number, sites, and angle of biopsies necessary to detect and exclude cancers which may become symptomatic or cause death is not known. The number of biopsies varies from sampling restricted to a palpable or ultrasound detected lesion, to systematic quadrant or sextant biopsies in patients with an elevated serum PSA. Investigation of sampling has been based on the relation between tumour volume and metastases.<sup>4</sup> Sextant biopsies of clay models have indicated that cancer would be detected in 36%, 44%, and 100% of cases when tumour occupies 2.5%, 5%, and 20% of the gland volume, respectively.<sup>5</sup> As a result of correlation of *in vitro* multiple core biopsies and tumour mapping of radical prostatectomy specimens, a minimum of six biopsies was advocated if tumour volume was to be reliably predicted. A stronger correlation was obtained with 10 biopsies including four from the anterior aspect.<sup>6</sup> The technology is available to allow the step-section tumour mapping of radical prostatectomy specimens to be constructed into a three dimensional model which may be subjected to simulated biopsies. Such

collaborative studies are being carried out by a Swedish-American group.

Protocols involving multiple prostatic biopsies for serum PSA detected cancer raise the possibility of diagnosing microscopic cancer unlikely to become symptomatic. In practice the grade, volume, and pathological stage of tumours in radical prostatectomy specimens suggests that 6–16% would be “clinically insignificant” as determined by these features.<sup>7–9</sup>

In the context of early diagnosis of carcinoma and future trials of androgen ablation therapy for the precursor lesion, the recognition of prostatic intraepithelial neoplasia (PIN) is important. The lesion and its relation to cancer has been clearly described.<sup>10</sup> Clinical management of high grade PIN (close surveillance or rebiopsy) relates to its concomitant association with invasive carcinoma in 30–100% of patients rebiopsied within a short interval.<sup>10</sup> However, many of the rebiopsy series were retrospectively derived from PSA screening projects. The significance of high grade PIN in a patient with a normal serum PSA has not been established.

The increase in prostatic biopsy referrals and requests from colleagues to audit such specimens indicate a level of diagnostic concern, possibly enhanced by perceived lack of practical educational support and external quality assessment that has followed other official screening programmes. However, the diagnosis, its differential with common pit-falls, and protocols for biopsy reports have been well described in the literature,<sup>11–12</sup> and a satisfactory  $\kappa$  statistic of benign-malignant decisions has been obtained.<sup>13</sup>

Currently, the important prognostic factors on biopsy are those predictive of cure by radical prostatectomy, thus, surrogate end points include tumour volume, extraglandular spread, seminal vesicle invasion and limit-positive disease in the radical specimen, and elevated serum PSA after radical surgery. On multivariate analysis Gleason sum scores and percentage of cancer in the biopsy core(s) proved independent factors for extraglandular spread and seminal vesicle invasion.<sup>14</sup> These results or slightly different features in other studies combined with preoperative serum PSA,<sup>9–15–16</sup> have been suggested as suitable models to define treatment groups. However, biopsy features do not provide adequate information on tumour behaviour in individual patients.<sup>17</sup> Under grading cancer on biopsy is common,<sup>18</sup> and while extensive tumour in a core may correlate with high volume disease, the reverse interpretation is not reliable.<sup>17</sup>

In the search for alternative prognostic markers, BCL-2, microvessel density, neuroendocrine cells, E-cadherin, P53, and androgen receptor mutation, and the application of interface cytogenetics are deemed of high priority for research support.<sup>19</sup> As prostatic carcinoma in radical specimens proves heterogenous from grading to cytogenetics the reliability of any prognostic feature obtained from needle biopsies may be limited by the inherent sampling problem. Future possibilities for more accurate prediction of the efficacy of radical surgery include better imaging techniques

and peripheral blood markers of disease stage. Among the latter, identification of PSA mRNA by reverse transcriptase polymerase chain reaction is promising<sup>20</sup> but controversial.<sup>21</sup>

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## Colorectal cancer reporting: are we failing the patient?

In the United Kingdom, about 25 000 cases of colorectal cancer occur each year and more than 80% of these will be treated by surgical resection. Thus the average laboratory can expect to receive at least 100 resections annually. Despite being a routine part of pathological practice, results from the Welsh audit undeniably demonstrate a disturbing poverty of pathological reporting of such resection specimens.<sup>1</sup> We believe that these results reflect a countrywide weakness of colorectal cancer pathological reporting. There have been audits performed in many regions of England and in Scotland, and these have shown broadly similar results. Disappointingly the quality of reporting seems to have improved little since the poor performance was highlighted more than 15 years ago.<sup>2</sup> What is most disturbing about the Welsh audit is the fact that so few hospitals and reports even fulfil the minimum dataset. This is of critical importance for individual patient prognosis, for the determination of postoperative adjuvant chemotherapy and radiotherapy, to provide an indicator of the quality of rectal surgery, and for the overall management of the disease.

Colorectal cancer pathological reporting has received much publicity in the past 15 years. Why, then, is the reporting not even fulfilling these minimum standards? We believe that much of the responsibility for these deficiencies can be laid at the heart of the pathological establishment, in education of pathologists, and the attitude of senior staff towards the macroscopic assessment of specimens. There is no doubt that if the "cut-up" of a colorectal cancer specimen is poor then no amount of sophisticated microscopic assessment can redeem the position. Lymph node harvesting, evaluation of local spread, and the determination of margin and serosal involvement all demand diligent assessment and dissection of the specimen and rely

little on microscopic evaluation. However, macroscopic assessment is still poorly taught and certainly does not figure highly in Royal College examinations. Prioritisation in pathological practice remains with microscopic assessment and in many centres the cut-up is still largely the province of junior pathologists. We can understand that pathologists are not inclined towards the dissection of a poorly prepared colorectal cancer specimen but current practice demands that such specimens are adequately prepared so that the maximum amount of information can be derived. While the attitude of most pathologists towards the Ashworth dilemma<sup>3</sup> was wholesale condemnation, the proposal that well trained MLSOs should dissect specimens may require further consideration if pathologists do not have the time or motivation to assess such specimens adequately.

The importance of the pathological reporting of colorectal cancers has increased enormously for two main reasons: first, the recognition of the significance of involvement of circumferential (radial, mesorectal) margins in rectal cancer with the potential for the pathologist to audit the technical quality of the surgery; and second, the influence of pathological results on the decision to institute adjuvant therapy. The results of assessment of circumferential margin involvement were particularly poor in the Welsh audit. Yet this is the major determinant of local recurrence in rectal cancer, a feature with a profound influence on morbidity and mortality.<sup>4-6</sup> Failure to identify circumferential margin involvement in rectal cancer denies the patient the chance to be considered for postoperative radiotherapy which might help to salvage the situation. It has been shown how few useful data can be gained from the assessment of proximal and distal margins of excision<sup>7</sup>: pathologists should instead concentrate on the assessment of circumferential margins and the serosal surface that